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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/931,112	08/17/2001	Marshall Z. Schwartz	06510003PB	3767

7590 10/21/2003

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EXAMINER	
BORIN, MICHAEL L	
ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 10/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/931,112	SCHWARTZ, MARSHALL Z.	
	Examiner	Art Unit	
	Michael Borin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Claims

1. The Examiner acknowledges preliminary amendment filed 08/17/2001 canceling claims 1-6, 13-20. Claims pending are 7-12. In view of this Preliminary amendment, which was inadvertently overlooked at the time of issuing restriction requirement, both the restriction requirement mailed 05/05/2003, and the response to it filed 08/01/2003, are moot.

Title, Abstract

2. The title and abstract of the invention are not descriptive. The title and abstract do not reflect the elected invention. A new title and abstract are required which are clearly indicative of the invention to which the elected claims are directed.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said

subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

3. Claims 7-12 are rejected under 35 U.S.C. 103(a) as being obvious over Zushi (Am. J. Physiol.270, G757-G762, 1996) and Ishii (JP 08231418) and Fukamachi (Biochem. Biophys. Research Communication, 205 (2), 1445-1451) and Halttunen (Gastroenterology, 111, 1252-1262, 1996).

The instant invention is drawn to method of treating a patient having intestinal mucosal damage comprising decreasing mucosal damage in a small intestine by administering an effective dose of hepatocyte growth factor (HGF).

Zushi

Zushi et al teach that HGF accelerate intestinal epithelial restitution (wound resealing). See Abstract. Authors use *in vitro* cell culture model which is accepted in the art as a model of differentiation of intestinal epithelium and epithelial absorption. See p. G757, right column, end of second para.

Ishii

Ishii teaches that HGF promotes intestinal cell proliferation and motility and is useful for prevention or treatment of intestinal diseases such as ulcerous colitis and inflammatory colitis. See Abstract.

Fukamachi

Fukamachi describes that HGF stimulates growth of various types of cells including the growth of gastrointestinal epithelial cells. See Abstract, Fig. 1., Discussion section.

Halttunen

Halttunen et al use an *in vitro* model of T84 epithelial cells of intestinal epithelial cells co-cultured with fibroblasts. The authors emphasize that because of the complexity of the intestinal mucosa and difficulties in *in vivo* studies the cell culture model used in the study is a comprehensive model of intestine. (p. 1253, paragraphs 1-2). The results (p. 1257) demonstrate that HGF stimulates proliferation of intestinal cells.

Taken together, the prior art demonstrates that HGF, in several cell culture models, stimulate proliferation of intestinal cells and augmentation of their motility. Proliferation of intestinal cell will be manifested in an increase in intestinal tissue mass

and will result in an increase in intestinal absorptive functions. This is because intestinal absorption is a result of combination of multiple molecular transport mechanisms operating in intestinal cells. Each intestinal cell has a finite transport capability, and consequently, intestinal absorption capability is determined, in part, by the amount of intestinal cells in the intestine. Therefore, an increase in the amount of intestinal cells will result in an increase in their total absorptive capability, and it would be obvious to expect that proliferation of the intestinal cells will cause an increase in the intestinal absorptive functions. In addition, proliferation of intestinal cells will, naturally, result in an increase in intestinal tissue mass. As there is a need, for certain disorder conditions, to increase intestinal absorptive functions and/or intestinal tissue mass, a practitioner would be motivated to use HGF to achieve these desired effects because *in vitro* studies on adequate models strongly suggest that HGF would cause proliferation and growth of intestinal cells *in vivo*.

Although the referenced prior art does not demonstrate, directly, the *in vivo* effects of HGF as claimed, the references used demonstrate that HGF has similar proliferative effect on different cell systems each of which is an adequate model of *in vivo* conditions. Thus, Zushi reference teaches that "Caca-2 cell line has been extensively used as a model of differentiated normal intestinal epithelium in examination of the mechanisms of absorption, electrolyte transport, and restitution" (p.G757, right column, end of second

paragraph). *In vitro* testing may establish a practical utility of a compound if *in vitro* data are reasonably predictive of the therapeutic utility. The cell models described in the references are all accepted as reasonably correlated to the *in vivo* conditions and pharmacological activity is reasonably based on the probative evidence.

Therefore, is would have been *prima facie* obvious, however, to one skilled in the pertinent art that such effect of HGF demonstrated on cellular level would *in vivo* translate into the increase in intestinal tissue mass and enhancement of intestinal functions, such as absorbtive function. This, in turn would result in decrease in the extent of mucosal damage iin the diseased intestine, i.e., in the effect instantly claimed. In view of the above, one of ordinary skill in the art would have been motivated to use HGF a therapeutic agent for increasing intestinal tissue mass and augmenting its functions. The invention as a whole would have been *prima facie* obvious to one having ordinary skills in the art at the time the invention was made, especially in the absence of any evidence to the contrary.

The references do not expressly teach the claimed concentration ranges. Absent some teaching to the contrary however, the determination of particular ranges employed is within the skill of the ordinary worker as a part of the process of normal optimization.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 7-12 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 5972887. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of 5972887 are drawn to use of HGF to increase intestinal tissue mass of a small intestine and intestinal mucosal substrate absorptive functions of a small intestine in patients suffering from intestinal malfunction and damage. The dosages of HGF are the same as instantly claimed (see claims 3, 9, for example). It would be obvious that increase in intestinal tissue mass and in intestinal mucosal substrate absorptive functions would result in alleviating intestinal mucosal damage as instantly claimed.

Conclusion.

5. No claims are allowed.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (703) 305-4506. Dr. Borin can normally be reached between the hours of 8:30 A.M. to 5:00 P.M. EST Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Michael Woodward, can be reached on (703) 308-4028. The fax telephone number for this group is (703) 305-3014.

Any inquiry of a general nature or relating the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

October 14, 2003

MICHAEL BORIN, PH.D
PRIMARY EXAMINER

mlb